ORIGINAL ARTICLE

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Chronic kidney disease in patients with acute myocardial infarction without ST segment elevation: therapeutic nihilism?

Doença renal crónica em doentes com enfarte agudo do miocárdio sem elevação do segmento ST: niilismo terapêutico?

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ABSTRACT

Background: Chronic kidney disease is an independent risk factor for mortality after acute coronary syndrome. Our aim was to characterize the in-hospital management and outcomes of patients with chronic kidney disease in the setting of non-ST-segment elevation myocardial infarction. **Methods**: This is a single centre, prospective and observational study, including 230 consecutive patients admitted with the diagnosis of non-ST-segment elevation myocardial infarction. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease Study formula and in-hospital therapies and outcomes were recorded. **Results**: Overall, 25.7% of patients had moderate to severe chronic kidney disease. Patients with chronic kidney disease were less likely to undergo coronary angiography (27% vs. 81%, $p < 0.001$) and receive less evidence-based therapies, including aspirin (86.4% vs. 98.8%, $p < 0.001$), clopidogrel (74.6% vs. 90.6%, $p = 0.002$), angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker (54.2% vs. 90.6%, $p < 0.001$) or anticoagulant therapy (83.1% vs. 95.9%, $p = 0.001$). In addition, the in-hospital mortality was higher for patients with chronic kidney disease (15.3% vs. 2.9%; $p = 0.002$). **Conclusion**: Non-ST-segment elevation myocardial infarction patients with chronic kidney disease have higher in-hospital mortality. The underuse of evidence-based therapies and interventions can help to explain these results.

Key-words: Acute myocardial infarction; chronic kidney disease.

RESUMO

Introdução: A doença renal crónica é um fator de risco independente para mortalidade após síndrome coronário agudo. O objetivo deste estudo foi caracterizar o tratamento, complicações e mortalidade intra-hospitalar dos doentes com doença renal crónica internados no contexto de enfarte agudo do miocárdio

sem elevação do segmento ST. **Métodos**: Estudo unicêntrico, observacional e prospetivo que incluiu 230 doentes internados com o diagnóstico de enfarte agudo do miocárdio sem elevação do segmento ST. A taxa de filtração glomerular foi estimada pela fórmula *Modification of Diet in Renal Disease Study* e foi avaliado o tratamento, complicações e mortalidade intra-hospitalar. **Resultados**: Do total de doentes admitidos no estudo, 25.7% apresentavam doença renal crónica moderada a grave. Os doentes com doença renal crónica foram menos submetidos a cateterismo cardíaco (27% *vs*. 81%, $p < 0.001$) e foram menos medicados com terapêutica baseada na evidência, nomeadamente aspirina (86.4% *vs*. 98.8%, $p < 0.001$), clopidogrel (74.6% *vs*. 90.6%, $p = 0.002$), inibidor da enzima de conversão da angiotensina e/ou antagonista do receptor da angiotensina II (54.2% *vs*. 90.6%, $p < 0.001$) e anticoagulantes (83.1% *vs*. 95.9%, $p = 0.001$). Os doentes com doença renal crónica apresentaram mortalidade intra-hospitalar superior (15.3% *vs*. 2.9%; $p = 0.002$). **Conclusão**: Neste estudo os doentes com enfarte agudo do miocárdio sem elevação do segmento ST e doença renal crónica apresentam mortalidade intra-hospitalar superior. A subutilização de terapêutica baseada na evidência poderá ajudar a explicar estes resultados.

Palavras-chave: Doença renal crónica; enfarte agudo do miocárdio.

INTRODUCTION

Chronic kidney disease (CKD) and acute coronary syndrome (ACS) are highly prevalent and widespread diseases[1,2]. Approximately 25% to 40% of all patients with non-ST-segment elevation myocardial infarction (NSTEMI) have at least moderately reduced renal function[3,4].

Chronic kidney disease is a recognized independent risk factor for early and late mortality after ACS[5-7]. Higher prevalence of other comorbidities, like hypertension and diabetes *mellitus*, diagnostic challenges because of the atypical presentation, and biological factors that promote and accelerate cardiovascular disease, are common among patients with CKD and contribute to the poor outcome of ACS in this specific population[8,9]. Moreover, several registries report underuse of evidence-based therapies in this population[10].

The aim of the present study is to characterize the in-hospital management and outcomes of patients with CKD in the setting of NSTEMI.

METHODS

This is a single centre, prospective and observational study, including consecutive patients admitted to the emergency department of Hospital Pedro Hispano EPE, with the diagnosis of NSTEMI, between the 1st January and the 31st December 2010. Only type 1 myocardial infarctions (MI) were included. The information was collected prospectively by physicians and more than 100 variables were studied. They included baseline characteristics, ECG changes, biochemical markers, in-hospital course and coronary angiography.

Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) Study formula[11], which includes creatinine, age, gender and race. Creatinine measurements for the 3-12 months before admission were used for eGFR calculation.

The diagnosis of CKD was considered if the eGFR was < 60 mL/min/1.73m^2 (K/DOQI stages 3 to 5)[12].

Previous data of stroke, MI, congestive heart failure (HF), chronic pulmonary disease, diabetes *mellitus*, hypertension (HT), dyslipidaemia and chronic medications were obtained from medical records or reported by the patients or their family.

Patients were treated according to the recommendations of the 2007 ACS guidelines[13], but the final decision of therapeutic options was the responsibility of the attending physician.

For coronary angiography we considered all patients who underwent coronary angiography during

the hospital stay, regardless if they were revascularized or not.

The main adverse events reported were reinfarction, malignant arrythmia, bradiarrythmia with pacemaker implantation, mechanical complications (including acute mitral regurgitation, interventricular septal rupture, cardiac tamponade and cardiac rupture), major bleeding (including intracranial, retroperitoneal or any haemorrhage requiring transfusion) and death.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation or median and interquartile range, according to their distribution. Continuous variables were compared between groups using unpaired *t*-test (for normally distributed variables) or the Mann-Whitney U-test (for non-normally distributed variables). Spearman´s rank correlation was used for the assessment of continuous variables.

Multivariable logistic regression model was used to study the association between coronary angiography and baseline characteristics and risk scores. Variables with clinically and statistically univariate relationships with coronary angiography were included in the multivariate model.

All reported probability values are two-tailed, and $p < 0.05$ was considered statistically significant. Analyses were performed with the IBM®SPSS® Statistics software package (version 20.0) (SPSS Inc, Chicago, IL, USA).

The authors had access to the data and take full responsibility for the results. All authors have read and agreed to the manuscript as written.

RESULTS

In total, 230 NSTEMI patients were included in the present analysis. Fifty nine patients (25.7%) had stages 3 to 5 CKD. The majority (88%) had stage 3 CKD (Table I). Baseline characteristics of patients with and without CKD are presented in Table II. Patients with CKD were older, more often diabetic, and more frequently had previous MI or heart failure. The CKD patients also had higher pre-treatment risk scores of death/MI (TIMI risk score; GRACE risk score) and bleeding (CRUSADE bleeding score) (Table II).

Table I

Patients' distribution for CKD stages according to KDOQI[12].

	n	
Stage 3	52	88.2
3a	29	49.2
3b	23	39
Stage 4	5	8.5
Stage 5	2	3.4

Table II

Patients' baseline characteristics and risk scores according to CKD status.

	No CKD	CKD	P value
Age, years	63 ± 13	70 ± 10	< 0.001
Women, %	27	37	0.158
Hypertension, %	68.4	91.2	< 0.001
Diabetes *mellitus*, %	29.2	57.6	< 0.001
Dislipemia, %	60.9	63.6	0.752
Prior MI, %	27.5	45.8	0.015
Prior HF, %	12.3	39	< 0.001
Prior Stroke, %	8.8	13.6	0.317
GRACE risk score*	123 [96-152]	159 [151-205]	< 0.001
TIMI risk score*	3 [2-4]	4 [2-5]	< 0.001
Crusade bleeding score*	25 [13-37]	53 [46-66]	< 0.001

* Presented as median. MI – Myocardial infarction; HF – Heart failure.

In-hospital treatment

Patients with CKD were less likely to undergo coronary angiography (27% with CKD vs. 81% without CKD, $p < 0.001$).

After adjustment for age, presence of diabetes *mellitus*, acute kidney injury and risk scores, CKD was an independent predictor for not submitting to coronary angiography ($p = 0.001$) (Table III).

Patients with CKD were also less likely to receive in-hospital evidence-based medical therapies, such as aspirin ($p < 0.001$), clopidogrel ($p = 0.002$), angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker ($p < 0.001$) or anticoagulant therapy ($p = 0.001$) (Table IV).

Table III

Multivariate model of predictors to not undergo coronary angiography.

	OR (95% CI)	P value
Age	0.95(0.92-0.98)	0.004
AKI	1.59(0.56-4.55)	0.386
Diabetes *mellitus*	0.99(0.43-2.29)	0.991
CKD	4.37(1.80-10.5)	0.001
GRACE risk score	0.99(0.99-1.00)	0.379
TIMI risk score	0.78(0.57-1.08)	0.138
Crusade bleeding score	0.98(0.96-1.01)	0.231

OR – Odds ratio; CI – Confidence interval; AKI – Acute Kidney Injury; CKD – Chronic Kidney Disease.

Table IV

In-hospital medical treatment by presence of CKD.

	No CKD	CKD	P value
Aspirin, %	98.8	86.4	< 0.001
Clopidogrel, %	90.6	74.6	0.002
ACEI and/or ARB, %	90.6	54.2	< 0.001
β -blockers, %	97.7	79.7	0.146
Statin, %	96.5	93.2	0.284
Anticoagulant, %	95.9	83.1	0.001
Glycoprotein IIb/IIIa inhibitor, %	51.5	43.7	0.595

ACEI – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin II receptor blocker.

For patients who underwent coronary angiography, the rates of the use of glycoprotein IIb/IIIa inhibitors were similar among those with and without CKD (Table IV).

In-hospital outcomes

There were no differences between groups concerning the major adverse events pre-defined in this study (Table V).

In the 154 patients who underwent coronary angiography, there were six cases (3.9%) of iodinated contrast induced nephropathy (CIN), five of which in patients with CKD ($p < 0.001$). In none of these five patients dialysis was needed.

Fourteen patients died during hospitalization due to cardiovascular events. In-hospital mortality was higher for patients with CKD [nine (15.3%) vs. 5 (2.9%); $p = 0.002$].

Table V

In-hospital major adverse events according to CKD status.

	No CKD	CKD	P value
Reinfarction	2	3	0.108
Malignant arrythmia	4	4	0.209
Bradiarrythmia with pacemaker implantation	3	0	0.572
Mechanical complications	1	0	1.00
Major bleeding	1	0	1.00
Death	5	9	0.002

DISCUSSION

Globally, 25.7% of patients had moderate to severe CKD in this study, which is consistent with the findings in the more contemporary data using MDRD equation[14].

Patients with CKD had more comorbidities than patients without CKD, and higher risk scores of reinfarction, death and bleeding. Despite their higher risk, CKD patients were less likely to receive evidence-based therapies and the presence of CKD was an independent predictor for not undergoing coronary angiography. This seems to be a paradox in the management of CKD patients with NSTEMI.

The lesser use of coronary angiography in CKD patients may be justified by the fear of worsening kidney function, but several authors have demonstrated that the benefit overcomes the risk[4,15-17]. Furthermore, the most recently published guidelines by the American College of Cardiology/American Heart Association for management of NSTEMI state that an early invasive strategy is a reasonable strategy in patients with mild and moderate CKD[18].

We found the same rates of CIN described in the literature[19] and these patients did not experience major adverse events, suggesting that CIN is not a valid reason to avoid iodinated contrast media investigations in this group of patients.

Some previous studies have demonstrated the underuse of evidence-based medical therapies in CKD patients[4,14] and have suggested that it could contribute to the higher mortality observed in this population.

On the other hand, a recent publication[1] concludes that treatment disparities related to CKD are most evident at top-performing hospitals, and the reasons for those findings need to be explored.

Our CKD patients also had underuse of all evidence-based therapies, but this was more evident with antithrombotic agents. We found a significantly decreased use of aspirin, clopidogrel and anticoagulant in CKD patients. Given that CKD patients also have higher risk scores for bleeding, one possible explanation for these differences is physicians' perception of bleeding risk in these patients, making them withhold antithrombotics prescription. The increased risk of bleeding in CKD patients may be related to intrinsic platelet dysfunction[20] and excessive dosing of medications [21].

Similarly, we found an underuse of ACEI and/or ARB. That could be explained by the higher rate of acute kidney injury at hospital admission in CKD patients (39% vs. 6.4%) and, once more, by the concern that these medications can deteriorate kidney function, even though benefits of ACEI and/or ARB are well documented in patients with reduced left ventricular ejection fraction[18].

No difference was seen between patients with or without CKD, concerning the rates of major in-hospital adverse events, except death. Indeed we did not register any episodes of major bleeding in CKD patients. The small number of patients and the small number of adverse events observed contribute for that fact.

The highest rates of in-hospital mortality observed in patients with CKD, when compared with those observed in patients without CKD, are concordant with previous reports[4,16,22]. Given our small sample, we can only speculate that the underuse of evidence based medications and procedures could be responsible for the higher in-hospital mortality in CKD patients.

Strengths and Limitations

The major strength of the present study includes the use of a Portuguese prospective cohort that reflects the reality of NSTEMI management in our country.

Furthermore, because of the organizational structure of this hospital unit, we had easy access to the previous creatinine determinations, so it was possible to ascertain more accurately the patients' actual renal function.

However, certain limitations are notable. This being a single centre analysis with a relatively small number of patients, it precludes definite conclusions about outcomes.

Finally, as we used MDRD Study formula that underestimates GFR in individuals with measured GFR ≥ 60 ml/min/1,73m2[23], and as we did not have information about other markers of kidney damage except for serum creatinine, we could not identify patients with CKD stages 1 and 2. Especially, we did not have information on albuminuria and proteinuria known as risk markers of cardiovascular events[24].

CONCLUSIONS

Chronic kidney disease patients presenting with NSTEMI have more comorbidities and higher risk scores of death and bleeding.

Data from this study suggests that patients with CKD receive fewer evidence-based therapies and have substantially higher in-hospital mortality rates. However, further research is warranted to define the relevance of undertreatment for the higher mortality seen in patients with CKD after NSTEMI.

Conflict of interest statement: None declared.

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